# Oliver-Sharpey Lectures

ON THE

# PRESENT CONDITION OF OUR KNOWLEDGE REGARDING THE FUNCTIONS OF THE SUPRARENAL CAPSULES.

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## LECTURE I.

No more congenial position can well be conceived for a physiologist than to be honoured by an invitation to address upon a physiological subject the College before whom the illustrious Harvey expounded the discovery which has been the starting-point of all physiological research. The congeniality of the position is for me enhanced by the fact that the great English teacher of physiology, Sharpey, in whose memory this lectureship was founded, was my honoured master, and that the founder of the lectures, Dr. George Oliver, was my collaborator in the research which has led me to select the suprarenal capsules as the subject of the present lectures.

### WILLIAM SHARPEY.

There must be many of my auditors who remember Sharpey and some who had the privilege of listening to his lectures. But since the death of Michael Foster, which we have so recently had to deplore, there is no one living who had so intimate a personal acquaintance with him as myself. It will not, therefore, I trust, seem inappropriate if I preface these lectures with a sketch of the career and character of a man who has exerted, directly or indirectly, a more profound influence upon British physiology than any of our countrymen since the time of Harvey.

It is curious to note that Sharpey was the son of a native of Folkestone, the birthplace of Harvey. Sharpey himself, however, was born in Arbroath, of a Scottish mother (in 1802), and his education was entirely Scottish. His father died before the son saw the light, and William Sharpey was brought up by his mother and her second husband, Dr. Arrott, a medical man in Arbroath, who became in all respects a second father to him. At the age of 15 he was sent to the University of Edinburgh as a student of Arts, and at 16 he began his medical studies in the same university and in the extramural school which is attached to it. At 19 he obtained the diploma of the College of Surgeons of Edinburgh; and in 1823, at the age of 21, he took the degree of M.D. in the university, the subject of his thesis being cancer of the stomach.

Although engaged for a short time in assisting his stepfather at Arbroath, Sharpey soon came to the conclusion that the study of anatomy and physiology would be more congenial to him than medical practice, and both before and after taking his degree he spent some years in the anatomical schools of London, Paris, and Berlin, besides undertaking a prolonged and mainly pedestrian tour in Switzerland and Northern Italy, visiting the great university centres in those countries and making acquaintance with many distinguished anatomists. In Berlin he worked assiduously at anatomy under Rudolphi, making full and minute dissections of all parts of the body and storing up in a retentive memory a mass of facts destined to be drawn upon with great profit in his subsequent teaching.

Having finished his *Wanderjähre*, Sharpey settled down in Edinburgh in 1829, devoting himself at first entirely to research, and subsequently (1831) becoming installed as an extramural lecturer on anatomy in association with his lifelong friend Allen Thomson, who took as his subject physiology. It is interesting to note that while Sharpey subsequently became a famous teacher of physiology, eventually Allen Thomson developed into a no less distinguished teacher of anatomy.

In 1836 Sharpey was invited to fill the Chair of Anatomy and Physiology in the new University of London, which was then about to be transformed into University College; this chair eventually developed into one of physiology alone. Here he at once made a mark as a teacher. His lectures were followed throughout with unabated interest by a long succession of students, for he held the Chair during thirty-eight years, and his influence in spreading a knowledge of the principles of physiology must have been immense. I believe that there is no actual teacher of physiology now living who sat under him except myself, but when it is remembered that Michael Foster, the founder of the Cambridge School of Biology, was his pupil and friend, and that Burdon-Sanderson came early in his career as a physiologist into intimate relations with him, it will be apparent how widespread was the influence which Sharpey's teaching has exerted upon the progress of physiology in this country.

And not only had he thus a large share in the promotion of physiological science, but indirectly the progress of scientific medicine and surgery owes much to his influence, for many who have since become eminent in those subjects were taught by him, and the character of their work has manifested the thoroughness of his teaching. It would be invidious to mention names—they will occur to all present. Some are still with us; fortunately, this is the case with the most eminent of all, Lister.

The secret of Sharpey's influence is to be found in the personal character of the man, which was reflected in his teaching, and gave to it the attributes which all successful teaching must possess: accuracy, clearness, and a due subordination of the several parts of a subject.

Sharpey's quality of accuracy is reflected in his researches. These were neither numerous nor extensive; but most of his observations have stood the test of time and criticism, which is, I fear, more than can be said for the contents of very many scientific memoirs. The best example of this is furnished by his account of the structure and development of bone, which was written for the fifth edition of *Quain's Anatomy*, and which, with little modification, still holds good for the eleventh edition of that work. He was a man of singularly sound judgement, kind disposition, and genial nature, qualities which procured for him the esteem of an extensive acquaintance and the affection of those who had the privilege of closer intimacy. He was Secretary to the Royal Society during nineteen years, and the initiation of the Catalogue of Scientific Papers, as well as important improvements in the constitution of the society, were largely due to his initiative. He died on April 11th, 1880, at the age of 78, and was buried within the abbey churchyard of his native town of Arbroath.

### HISTORY OF THE INVESTIGATION OF THE SUPRARENAL CAPSULES.

It is almost exactly forty years since I, then a young student of medicine, attended for the first time Sharpey's course of lectures on physiology. And this event—a momentous one in my own life, for it unquestionably was the means of determining my future career—brings me directly to the subject which I have chosen for these lectures—namely, the present condition of our knowledge regarding the suprarenal capsules. To understand the position at which our knowledge has arrived on this subject we must have something to compare it with, and for this purpose nothing can be better than a brief statement of the condition of knowledge regarding these bodies at the time of which I am speaking.

To illustrate this I have borrowed from the Museum of the Medical School of University College Hospital, by the kind permission of the Committee, the stuffed rats which are placed upon the table. The legend regarding these in the catalogue is as follows:

3415. Two stuffed rats. The white one had the spleen and suprarenal capsules extirpated when it was only a month old and quite small. It increased in size after the operation quite as fast as its fellows which had not been touched. The animal was killed when five months old, and no discoloration of the skin or hair could be detected. The lumbar and other lymphatic glands were found enlarged.

The piebald rat had the right adrenal removed and died on the seventh day. The organ was considerably enlarged. On microscopic examination it was found to be the seat of extensive tuberculous disease. At the *post mortem* it was found that the left suprarenal was quite healthy (4226).—Vide *British and Foreign Medico-Chirurgical Review*, 1858, vol. xxi, p. 204, Harley on the Suprarenal Capsules.

We need not trouble further about the piebald animal, but the albino may fairly be said to typify the then



[2474]

condition of knowledge—which was negative—regarding the organs we are dealing with. To understand how these experiments came to be conducted it is necessary to go back some thirteen years further, fifty-three years from now. In the year 1855, Addison, a Fellow of this College and Physician to Guy's Hospital, described the disease which bears his name. He showed that in man a certain group of symptoms occurs occasionally—fortunately, we may add, rarely: "anaemia, general languor or debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin," the disease being usually fatal. Pigmentation of the skin and of certain mucous membranes is the sign which is, perhaps, most characteristic of the disease and in many cases first attracts attention. It is, says Addison, "the great distinctive mark of this form of anaemia." Another of its most pronounced features is the profound asthenia, "which is out of all proportion to the general condition" (Osler). The symptoms were shown by Addison to be associated with destructive disease—usually tuberculous—of the suprarenal capsules.

Addison's monograph attracted immediate attention, and soon led to experiments upon these bodies. The earliest were by Brown Séquard (1856), who removed the capsules in various animals (dogs, cats, rabbits, and guinea-pigs), with an unfailingly fatal result—usually within twelve hours in adult animals, young animals surviving the operation somewhat longer. Removal of one capsule produced in some cases death within a few days, but in other cases had no obvious effect; when the second was removed, even after a long interval of time, the symptoms of total ablation rapidly showed themselves, although death followed less rapidly than after simultaneous removal of both capsules. The symptoms following the removal were those of Addison's disease, but more acute and without the pigmentation. Brown-Séquard supposed, and doubtless correctly, that the absence of pigmentation in these experiments is due to the rapidity with which a fatal result supervenes, for the formation of pigment must be a somewhat slow chemical process. More recent observers—Tizzoni, Nothnagel—who have succeeded in slowly destroying the suprarenals of animals by other means, such as crushing, state that they have been able to observe such pigmentation in the animals experimented on. Brown-Séquard's results were repeated by other observers; amongst these may be mentioned Phillipeaux, George Harley, and Schiff. Besides employing ordinary domestic animals, such as the cat and the dog, in which, as Brown-Séquard had done, they invariably obtained fatal results, these observers also selected for experiment the ordinary tame white rat, and one of these, operated upon by Harley, is now before you. It was by a curious chance that this animal was not employed by Brown-Séquard, because the rat happens to be the one common animal which is able to withstand complete removal of both suprarenal capsules. The reason for this was not at the time apparent, although it is now known, for the rat is exceptional in possessing in various parts at the back of the abdomen and pelvis numerous small glandular structures which are composed of cells having the characteristic features and functions of the cells of the suprarenal medulla. Harley, as well as Phillipeaux and others, accordingly found that a rat may indefinitely survive entire removal of the suprarenals, and although they had got contrary results with other animals, they put the fatal results down to injury to adjacent nerves and blood vessels, and, generalizing from the negative effect of removal in the rat, they came to the conclusion that these organs are not, as Brown-Séquard supposed, essential to life. They regarded the contrary results of Brown-Séquard as being also due to collateral injuries to adjacent nervous and other structures, and not to the absence of the suprarenal capsules. They were fortified in this opinion by the fact that in many of their cases death supervened after removal of one capsule only—a result by no means surprising when we remember the situation of the capsules, the fact that they were usually attacked from the peritoneal cavity, and that this was before the days of asepsis. We now know that Harley and the others were, in the conclusion they drew, wrong and Brown-Séquard right; but we can recognize that it was a natural conclusion to draw, and are not surprised that it was shared generally by physiologists, and amongst them by Sharpey, who must have witnessed the experiments, and not improbably had been consulted by Harley about them. Such negative results—their real cause being at that time not understood—had the effect for the nonce of so effectually obscuring the inferences to be drawn from ablation experiments upon this organ that it was not until a lapse of thirty years that experimentation upon the subject was recommenced. It is therefore a simple statement of fact that positive knowledge regarding the functions of the suprarenal capsules, as reflected by the teaching of the most prominent physiologists of the time, was forty years ago *nil;* while the information regarding these structures which has since accumulated is in all respects—as regards development, structure, and functions—so large that it would occupy the greater part of the time devoted to one of these lectures merely to enumerate the papers which have been published upon them, and upon important collateral questions which have been raised in the course of the investigations made to elucidate their functions.

The ball which was set rolling by Addison and Brown-Séquard in the middle of the last century was, after a prolonged period of rest, again started by Tizzoni (1884), and has been now kept going uninterruptedly for four and twenty years. Tizzoni himself, although obtaining a fatal result from complete removal, also in some cases got a like result from removal of one capsule, and was inclined to come to the same conclusion as that arrived at by the earlier experimenters—namely, that when death occurred it was due to an effect upon the nervous system, and that these organs are not essential to life. But before long Brown-Séquard's results were confirmed by many observers, among whom may especially be mentioned Dominicis (1894) and Langlois—who, partly in conjunction with Abelous (1891-2), partly in investigations carried out independently and with others (1893-7), performed a large number of partial and complete extirpations—always, in the case of the complete removal, with the same fatal result. Dr. George Oliver and I, in the course of the experiments to which I shall afterwards have to refer, and as accessory to them, also obtained similar results to those described by Brown-Séquard. The animals we employed were monkeys, dogs, cats, rabbits, and guinea-pigs. But the most extensive observations of this nature seem to be those of Strehl and Weiss (1901), who extirpated the suprarenals in as many as 114 animals, all of which died in times varying from four hours to five days with the symptoms characteristic of this deprivation.

It may, therefore, be admitted that the conclusion which Brown-Séquard arrived at in 1856—namely, that these organs are essential to life—has been abundantly justified, although their mode of action was not understood by him in the sense in which it is now for the most part conceded. Although he speaks of them as secreting glands, Brown-Séquard appears to have been of opinion that the cause of death on their removal is the accumulation of toxic substances in the blood. He considered that one of their functions consists in modifying a substance which is endowed with the property of being easily transformed into pigment, and that they prevent this transformation. In a later communication he ascribed the immunity of the white rat to its albinism—that is, its inability to produce pigment.

It is curious to notice that, in resuming the consideration of the subject thirty years later, Brown-Séquard considered that he was in error in regarding these organs as essential to life and in attributing death after their removal to suppression of their functions. He now (1887) believed that the fatal result was due to irritation of nerves as the result of the operation, an opinion which had been pretty general amongst those who immediately followed him, and who had failed—in the rat—to confirm his observations regarding the effects of complete removal in other animals.

Brown-Séquard did not conceive the idea that the fatality following complete extirpation might be due to suppression of an internal secretion, useful and even necessary in the economy, but regarded the main function of these organs as being for the prevention of the formation of a toxic body, and therefore as *antitoxic*—an opinion which seems to have had a marked influence upon the conclusions arrived at by physiologists, especially those of the French school, when interest in the subject became revived. And this, doubtless, led to the crystallization of the idea that there is present in the blood of animals deprived of suprarenals a definite toxin producing muscular paralysis, in the opinion of Langlois similar in action to curare (theory of autointoxication). But with the demonstration of the fact that the glands yield a substance which produces beneficial physiological effects, such as increased tone and contraction of the heart and muscles, blood vessels, and of the muscular system in general, the actual cause of the muscular weakness and lack of tonicity which results from their extirpation became manifest and led to the establishment of the theory of internal secretion.

But before this phase was arrived at the subject had been approached by another mode of experimentation, that of the determination of the physiological action of hypodermic injections of extracts of the capsular substance. The first to adopt this method of research was Pellacani (1879) associated later with Foà (1883). These observers were engaged in investigating the effects of organ extracts in determining the formation of coagula, and amongst other substances they injected a water extract of six suprarenal capsules of the ox into the auricular vein of a rabbit. The injection produced death by arrest of respiration within two minutes, preceded by rapid respirations, general convulsions, strong intestinal peristalsis, and dilatation of the pupil. Subcutaneous injections in other animals produced death within twenty-four hours. They believed death to be due to the formation of coagula *intra vitam*. It will be seen that the doses they dealt with were enormous. They made no observations upon the blood pressure. Pellacani and Foà's results were confirmed by various other Italian investigators—Marino Zucco, Dutti, Guarnceri—who concluded that the toxic material obtained from the capsules owed its activity to the presence of *neurin*. Dr. Oliver and I, however, later were able to show that neurin has entirely different physiological effects. Other observers (Tizzoni, 1884, Alexais and Arnaud, 1890-1) denied the pre-existence of a toxic substance, and regarded the toxic effects sometimes produced as due to some chemical change occurring in the capsules after removal from the body, or during the manipulations employed for the extraction of the supposed toxic substance. But the different results obtained by these observers seem rather to have been due to the varieties of animals chosen, and to the relative dosage of the extract. As Dr. Oliver and I subsequently found, the rabbit is more susceptible to subcutaneous injection of the extract than other laboratory animals, the lethal dose for some species being much greater. Lesage (1904), indeed, states that the lethal dose of adrenalin injected intravenously is 0.1 to 0.2 mg. per kg. for the dog, rabbit, and guinea-pig, and 0.5 to 0.8 mg. for the cat; but Taramasio (1902) found the lethal dose injected subcutaneously to be 0.02 g. per kg. for the guinea-pig and 0.01 g. for the rabbit. Further, it is found that in some animals with repeated doses a certain degree of immunity may be established. Swale Vincent (1898) obtained results leading to the same conclusion; he also showed that the toxic effects, like the physiological effects, are due to a substance contained in the medulla alone.

The final stage of our knowledge regarding the functions of these organs was entered when the effects of intravenous injections was investigated with the aid of the apparatus (manometer, oncometer, cardiometer) ordinarily in use in physiological laboratories. This was first attempted by Dr. George Oliver and myself, and the results were exhibited to the Physiological Society and published in its *Proceedings* in 1894. Investigations carried on by these methods showed that the gland extracts exert a potent influence upon the heart and blood vessels, and to a less degree upon skeletal muscles. Combined with the effects of subcutaneous injections, and with the fatal effects of extirpation of both capsules in a number of animals of different kinds, there was no room left for doubt that a substance is produced within the gland which is not only beneficial in maintaining the tone of muscular tissues, and particularly that of the vascular system, but which is, at least in most kinds of animals, essential to life, although in excessive doses it exhibits toxic properties. We felt justified in regarding this in the light of a true internal secretion, and in looking upon its absence in animals deprived of their suprarenal capsules, and in cases in the human subject in which both capsules were involved in disease, as the true cause of the symptoms which manifest themselves under these circumstances, not, as was then generally believed, the result of the action of a toxin accumulating in the blood, which it was the normal function of the suprarenals to destroy.

The position of the question in 1895 is thus summed up by Dr. Rolleston in his Goulstonian lectures. After first stating that three deductions are possible from the various researches which had up to that date been published regarding the physiology of the suprarenal bodies: (1) That they have no proper function, and are important only from their close relation to the sympathetic; (2) that they are excreting glands, removing pigment and toxins from the circulation; (3) that they are secretory glands, providing an internal secretion which is of use in the economy, he continues: "the evidence is sufficiently strong to warrant the conclusion that the adrenal bodies are functional glands," and that "Addison's disease is due to an inadequate supply of suprarenal secretion."

### STRUCTURE AND DEVELOPMENT OF SUPRARENAL CAPSULES.

Before entering into details regarding the physiological effects of this internal secretion of the suprarenals it may be of interest to give a brief account of certain special features which are exhibited in the structure and development of these organs. The general structure of the suprarenals in man and mammals is well known. Each is composed of a broad, striated (in section), yellowish cortex, and a deep-red medulla, the colour of the latter being due to blood in its sinus-like vessels. Between cortex and medulla is a boundary layer, usually reckoned with the cortex under the name of zona reticularis, and developed along with it, but differing both from it and from the medulla in arrangement of blood vessels, and to some extent in the appearance of its cells. The cells of the cortex are epithelium-like, are arranged in solid columns with blood vessels running in connective tissue between them, but not penetrating into the columns, and contain a fatty or lipoid substance, which imparts to the cortex its yellow tint. The course of the blood stream is from the surface towards the medulla. The cortical columns near the surface may exhibit a semitubular arrangement; their cells in some animals are long and cylindrical. In the boundary layer (zona reticularis) of the cortex the cell columns have a more open arrangement, they are separated by vascular spaces, and in some animals are characterized by the presence in the cells of a special brown pigment. The cells of the medulla are also epithelium-like; they are set vertically around the vascular spaces, which appear to be not true capillaries, but to have a sinusoid character, like those of the liver. The blood is collected from these spaces by veins most of which join to form the capsular vein which emerges from a groove in the anterior surface of the gland. The blood which flows from the gland contains distinctly more oxygen and less carbon dioxide than ordinary venous blood (Langlois and Chassevant, 1893). It also contains a larger amount of the active principle of the organ than ordinary blood; there is therefore no doubt that this material leaves the organ by the blood vessels. This is corroborated by histological evidence. The cells of the medulla stain intensely brown with chromic acid or its salts (Henle); they and similar staining cells found in other parts (sympathetic ganglia, coccygeal gland) have therefore been termed chromophil cells (Stilling, 1890), or chromaffin cells (Kohn, 1898). Granules or globules of a material yielding this reaction have been described not only within the cells of the medulla (Stilling, 1887), but also in the blood within the medullary sinuses (Gottlieb, 1883; Pfaundler, 1892; Manasse, 1895; Carlier, 1893; Auld, 1894), and in that of the suprarenal vein. There is, therefore, strong histological evidence that the cells of the medulla pass a secreted substance into the blood.

Many observers have described sympathetic ganglion cells within the medulla, but their existence has been denied by others. There is apparently considerable variation in this respect in different species of animals; they may be absent or present, and may be scattered or grouped into small ganglia. In any case they lie in the course of nerves which the gland receives from the sympathetic. Biedl (1897) states that stimulation of the splanchnics causes both an increased flow of blood through the gland (due to excitation of vaso-dilators) and an increased formation of the active material of the medulla (due to excitation of secretory fibres); the secretion and blood flow are therefore, as with ordinary secreting glands, governed from the central nervous system.

The comparative anatomy of the suprarenals has been investigated most satisfactorily by Swale Vincent (1898), who has described the structure and relations of these organs in various fishes, in tailed and tailless amphibia, in reptiles, birds, and several mammals. The most important of these observations from the point of view of their physiology is that in elasmobranch fishes the cortex and medulla are represented by two entirely distinct sets of glandular organs. The cortex of higher vertebrata is represented by the so-called *interrenal body*—"an ochre-yellow, rod-shaped body, paired in the rays, unpaired in the sharks, lying usually in the region of the posterior part of the kidney," and having the appearance microscopically of a secreting gland, but without ducts. The medulla, on the other hand, is represented by paired bodies, segmentally arranged, extending on each side of the vertebral column from the sinus of Monro to the posterior end of the kidney. The paired bodies are closely related to the sympathetic ganglia, have a superficial layer of non-chromophil cells and a central mass of chromophil cells, and also possess cells which appear to be transitional to sympathetic nerve cells. F. Balfour (1878) first put forward the view that these paired organs represent the medulla of the mammalian capsules, and the interrenal body the cortex; Vincent found by experiment that the paired bodies yield an extract which produces the same physiological effects as suprarenal medulla. In other fishes no organs representing the medulla have hitherto been found. The suprarenals are represented in teleostei by paired, roundish pink bodies (corpuscles of Stannius) attached to the kidney near its posterior extremity. Microscopically they resemble suprarenal cortex in structure, and their extracts have no physiological activity (Moore and Vincent, 1898). Swale Vincent removed these bodies in the eel, and three specimens survived the removal 28, 64, and 119 days respectively, whereas the longest time that a frog will survive complete extirpation of its adrenals is 12 or 13 days (Abelous and Langlois). In ganoids similar bodies lie embedded in the substance of the kidney. In amphibia both cortex and medulla are represented as occurring in small yellow masses or streaks adherent to the kidney, each mass containing always both cortex and medulla, the latter lying next to the kidney substance and possessing chromophil cells. These yield a physiologically active extract. The medulla in urodela is intimately related to the sympathetic ganglia, and there are transitions between the sympathetic cells and those of the medulla (Leydig, 1853; Vincent, 1898).

In reptiles and birds the suprarenals are in close anatomical relation, not with the kidneys but with the reproductive glands. The cortical part is formed of columns; medullary chromophil cells are distributed throughout it in isolated masses of various sizes and shapes, but most of the medulla forms a layer along the dorsal surface of the organ.

In birds the cortex and medulla are more intimately mixed than in any other animals, and the medulla is more abundant in proportion. As Vincent remarks, it is interesting to note in this relation that birds have a very high blood pressure. There are also intermediate cells between those of the sympathetic ganglia and those of the medulla. It may here be remarked that the terms *cortex* and *medulla*, although here used to denote the two specific parts of the suprarenals, are in their relationship to one another only applicable to mammals, in which alone the medulla is enclosed by cortex.

In one invertebrate only, up to the present, has any evidence been forthcoming of the existence of structures corresponding, at least physiologically, to the capsules of vertebrata. Roaf and Nierenstein (1907) have obtained from the hypobranchial gland of a mollusc (*Purpura lapillus*) an extract which both chemically and physiologically resembles in its action the active substance of the vertebrate suprarenal medulla. But the identity of the substance with adrenalin is denied by Dubois (1907), who seems to have previously subjected this gland to investigation. Vincent was able to obtain no such reactions as are given by suprarenal medulla from certain cells within the nervous system of *Palidina vivipara*, which Leydig had conjectured might represent suprarenal tissue.

*Development.*—Balfour and Mitsukuri (1881) described a separate origin for cortex and medulla, the former being developed from mesoderm, the latter from the same blastema as the sympathetic ganglia. This view is now universally conceded. Actually the cortex is derived from the mesodermic epithelium which covers the mesial aspect of the forepart of the Wolffian body, in front of the germinal epithelium, appearing first as a series of buds which grow together. The cells become arranged in columns, and the three series are early visible. In an embryo of 15.5 mm. it is depicted by Bryce (*Quain's Anatomy*, eleventh edition, 1908) as a rounded mass (on section) with sinus-like vessels in its central part and extending towards its attachment; they open into a central venule, as in a liver lobule. Between this organ and the aorta are masses of embryonic sympathetic cells, and groups of these grow into the gland. These have, like the sympathetic generally, been derived from neural ectoderm, but they are not yet differentiated into definite nerve cells. Those which grow into the gland do not for the most part undergo this differentiation at all, but are transformed into the cells of the medulla, which becomes marked off from the cortex in the fourth month. Ultimately they acquire chromophil substance; it is stated that this is not actually found in them in man until some little time after birth (Svehla, 1900; Moore and Purinton, 1900). But it occurs in the embryos of ox and sheep long before birth. It is well known that the suprarenals are relatively large throughout fetal life; this must have some functional significance, but what it is is unknown. It probably concerns the cortical substance.

Some cells of the sympathetic ganglia which differentiate into chromophil cells may remain as such within the ganglia, and occasionally small independent masses occur in the neighbourhood of the suprarenal or elsewhere at the back of the abdomen. As has already been stated, these are constantly present in the rat, and doubtless account for the fact that this animal can more readily than any other survive the extirpation of both capsules. Hence the results of Harley and others, as typified by the stuffed animals in the case before you.

### WHAT IS THE USE OF THE SUPRARENAL GLANDS?

In 1716 the Academy of Sciences of Bordeaux proposed as the subject of a prize, "What is the use of the suprarenal glands?" The competing essays were submitted to Montesquieu, the celebrated author of *Lettres Persanes* (a satirical description of French society and politics); *Causes de la Grandeur des Romains et de leur Décadence; De l'Esprit des Lois* (which, although published anonymously and put on the *Index Purgatorius*, passed through twenty-two editions in less than two years); *Défense de l'Esprit des Lois; Lysimaque*, a dialogue on despotism; and a novel termed *Arsace and Isménie*. Montesquieu had not yet attained to literary fame, but was a young man of 27. Nevertheless he had been made Counsellor of the *Parlement* of Bordeaux two years previously, and was at this time its President. It is recorded of him that although he discharged the duties of his office faithfully, he by preference devoted himself to researches on the physical characters of bodies, on sound and the causation of echoes, and on physiological problems such as the use of the renal (? suprarenal) glands. It is therefore probable that the subject of the essay had been suggested by him.

Montesquieu's report is curiously satirical. He commences with an account of the views which up to that time had been entertained regarding the function of these bodies (I quote from Langlois):

> Some have imagined that they (the capsules) are placed in the situation where they occur in order to hold up the stomach, which would otherwise press too hard upon the renal arteries; others to strengthen and consolidate the venous plexus which is in contact with them; conclusions which, says Montesquieu, appear to have escaped the ancients, who were content with simply expressing ignorance of the functions of these glands.
>
> Gaspard Bartholin was the first to relieve them from the stigma of performing so menial an office and to render them more worthy of the attention of savants. He is of opinion that a humour which he terms "black bile" (atrabilious humour) is preserved within their cavity, and believes that there exists a communication between the capsules and the kidneys, the atrabilious humour serving to dilute the urine.

Some anatomists, such as Spigelius, teach that the only use of the capsules is to collect the humidities which leak out of the great vessels which surround them; while others have held that a bilious juice is formed within them, and being carried to the heart, mingles with acidity which is there present and excites fermentation, this being the cause of the heart's movements; others, again, consider that the humour within the capsules is nothing more than the lacteal juice which is distributed by the mesenteric glands.

Montesquieu then proceeds with the analysis of the memoirs which were presented to the learned Academy of Sciences.

We have one author who affirms the existence of two kinds of bile; one, grosser, secreted by the liver; the other more subtile secreted by the kidneys with the aid of a ferment. This ferment flows from the capsules through ducts the existence of which is completely unknown to us and as to which, adds Montesquieu, we are threatened with perpetual ignorance.

Another describes to us two small canals which serve to carry the liquids which are found in the cavity of the capsule into the vein which belongs to it; this humour, which many experiments lead us to believe of an alkaline nature, plays, according to our author, the part of restoring fluidity to the blood which is returning from the kidney, and which has parted with its serosity in the formation of the urine.

Another competitor who begins by giving "*assez heureusement*" a description of the difference between conglobate and conglomerate glands, puts the suprarenal glands into the category of conglobates. He believes that they are nothing but a continuity of blood vessels within which, as within so many filters, the blood becomes more subtile. . . . The reason why there are no ducts to these glands, nor in any conglobate glands, is that there is no question of their separating liquids from the blood, but only of effecting the process of subtilization.

Finally after declaring that no single memoir amongst those submitted to his judgement can be looked upon as capable of satisfying the legitimate curiosity of the Academy, Montesquieu concludes:

Perhaps chance may some day effect what all these careful labours have been unable to perform.

And after a lapse of 177 years chance effected this result and enabled some sort of reasonable reply to be given to the question which was enunciated in 1716 by the Academy of Bordeaux, "What is the use of the suprarenal glands?"

In the autumn of 1893 there called upon me in my laboratory in University College a gentleman who was personally unknown to me, but with whom I had a common bond of interest—seeing that we had both been pupils of Sharpey, whose chair I at that time had the honour to occupy. I found that my visitor was Dr. George Oliver, already distinguished not only as a specialist in his particular branch of medical practice, but also for his clinical applications of physiological methods. Dr. Oliver was desirous of discussing with me the results which he had been obtaining from the exhibition by the mouth of extracts from certain animal tissues, and the effects which these had in his hands produced upon the blood vessels of man, as investigated by two instruments which he had devised—one of them, the haemadynamometer, intended to read variations in blood pressure, and the other, the arteriometer, for measuring with exactness the lumen of the radial or any superficial artery. Dr. Oliver had ascertained, or believed he had ascertained, by the use of these instruments, that glycerin extracts of some organs produce diminution in calibre of the arteries and increase of pulse tension, of others the reverse effect.

Although these conclusions were interesting, it was easy to see that results which were obtained under mechanical conditions which were somewhat complex and not easy of interpretation, could not be expected to decide an important physiological question of this nature, and that it was essential, in order to obtain exact knowledge of the action, if any, of such extracts, to conduct the investigations with the employment of all the means at the disposal of the modern physiologist. With the suggestion that we should undertake such an investigation Dr. Oliver promptly agreed, and it was then and there arranged to devote that winter to a thorough examination of the physiological effects of such extracts.

The result of this conjunction of effort, brought about by the fortunate chance foreseen by old Montesquieu, speedily showed that, whilst many of the extracts which had been dealt with clinically by Oliver were inert or at any rate not specific in their action, the suprarenal capsules, and to a less extent the pituitary body, yield to glycerine and to water and saline solutions principles which have an extraordinary effect upon the tone of the heart and arteries, transcending that of any known drug. We therefore decided to confine our attention during the time at our disposal in that winter to investigating the details of this action, and in the following March we were in a position to bring our results, which were already fairly complete, to the notice of the Physiological Society. In the meantime Mr. B. Moore, who is now Professor of Bio-Chemistry in the University of Liverpool, set to work to endeavour to isolate the active principle of the extract and to determine its chemical relationships. Although neither Moore nor other chemists who in various countries busied themselves with the solution of the same problem at the time succeeded in obtaining the active principle in a completely isolated condition, sufficient evidence was forthcoming to prove that it is a substance of relatively simple constitution. We had, in fact, already determined that it may be boiled for a short time without deterioration (although a temperature of 140° C. is said to destroy the blood-pressure raising principle, and, according to Gürber, to reverse the action of the extract); that it is dialysable and insoluble in absolute alcohol, and is not destroyed by acids or by the gastric juice. Moore found it to be identical with a powerfully reducing substance, first described by Vulpian (1857), in the medulla of the organ, and giving a characteristic colour reaction with oxidizing agents. Abel, of the Johns Hopkins University, and other physiological chemists who continued these investigations before long succeeded in obtaining crystallizable compounds of the active substance, and in determining a definite formula for it; Abel suggested for the substance the name epinephrin. Somewhat later (January, 1901), Takamine, a Japanese chemist, settled in New York, and independently Aldrich (August, 1901), worked out a method for the complete isolation of the active principle in a crystalline form (rhombic plates or needles), and Takamine gave to this product the name adrenalin. Other designations for the same substance are sphygmogenin (Fraenkel), suprarenin (v. Furth) and hemisine, although the one which is most commonly employed, and by which it is best known, is adrenalin. It is, however, for various reasons advisable to adopt a name which has no commercial attachments, which "adrenalin" seems to have acquired; and, since it is hardly possible to use a term which will signify the precise chemical constitution of the active substance, this constitution being somewhat complicated,* it would, I think, be well to substitute the term "adrenin" for the proprietary name "adrenalin."

An adrenin or adrenalin which has been produced synthetically in the laboratory by Stoltz (1907)—other substances nearly allied in constitution and action, but not identical, having been previously obtained by synthetic processes by Friedmann, Stoltz himself, and Dakin—is said by Hofmann (1907) to show all the activity of the natural substance. But Professor Cushny, who has tested it physiologically, informs me that the activity of the artificial adrenalin is very inferior to that of the natural product.

Nothing is certainly known as to the substances from which adrenin is formed in the organism, but W. L. Halle suggests (1906) that one of these may be tyrosine, which undergoes transformation into adrenin under the influence of a ferment in the suprarenal. In support of this conclusion, he found that when two portions of emulsion of fresh ox or pig suprarenal were taken, to one of them tyrosine being added, both being kept, with addition of toluol to prevent putrefaction, for six days in an incubator, the sample containing the tyrosine was found to have from 14 to 33 per cent. more adrenin than the control.

* The empirical formula which is given for adrenalin is $C_9H_{13}NO_3$. The constitution of the artificial product obtained by Stoltz is dioxyphenyl-ethanol-methylamin.

UNDER the will of the late Mr. Edmund Richardson the following institutions each receive a sum of 200 guineas: Charing Cross Hospital, the London Hospital, Middlesex Hospital, Brompton Cancer Hospital, University College Hospital, the Consumption Hospital, Fulham Road; the Royal Hospital for Incurables, the North-West London Hospital, the Royal Free Hospital, the Hospital for Sick Children, Great Ormond Street; and the Royal National Orthopaedic Hospital.